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(54) **ANTIGEN-BINDING CONSTRUCTS TARGETING HER2**

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(57) **ABSTRACT**

Described herein are high affinity antigen binding constructs, e.g., antibodies, directed to the ECD2 domain of HER2. The antigen-binding constructs comprise at least one antigen-binding polypeptide construct that binds to ECD2 of HER2 (HER2 ECD2) with increased affinity compared to a wild-type 2C4 antibody. Such antigen-binding polypeptide constructs comprise one or more amino acid modifications in the framework region and/or CDRs compared to the amino acid sequence of a wild-type 2C4 antibody that increase affinity of the antigen-binding polypeptide construct for ECD2 by 2-fold or greater. The antigen-binding constructs can inhibit the growth of HER2-expressing breast cancer cells and gastric cancer cells. Antigen-binding constructs in biparatopic format are internalized in HER2-expressing cells.

Specification includes a Sequence Listing.